Remarks

The final Office Action mailed March 18, 2009, has been received and reviewed. Claims 1, 3 and 5 having been amended, and claims 2, 4, 6 and 43 having been canceled, without prejudice, the pending claims are claims 1, 3, 5, 7, 8, 21-29 and 32-35. Reconsideration and withdrawal of the rejections are respectfully requested.

Rejection 35 U.S.C. §112, Second Paragraph

The Office rejected claim 21 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the term "peptidomimetic" was found to lack antecedent basis.

Claim 21 has been amended to delete recitation of the term "peptidomimetic." Reconsideration and withdrawal of the rejection of claim 21 under 35 U.S.C. §112, second paragraph, is accordingly requested.

Rejection under 35 U.S.C. §102(b)

The Office maintained the rejection of claims 5, 8, 22-26, and 32 under 35 U.S.C. §102(b) as being clearly anticipated by Low et al. (WO 90/12096). This rejection is respectfully traversed.

Applicant notes at the outset that in the final Office Action mailed March 18, 2009, the Office appears to have inadvertently made a misstatement concerning claims 1-4, 6, 7 and 21, stating erroneously that the claims are drawn to a method that provides for the *presence* of a membrane-permeabilizing agent. The claims actually recite the *absence* of a membrane-permeablizing agent. Applicant assumes that the Office did, in fact, mean "absence" since Applicant's previous argument, based on the recitation of the absence of a membrane-permeabilizing agent, was sufficient to overcome the rejection for claims 3, 4, 6 and 7. If

Applicant is incorrect in this assumption, Applicant kindly requests that the finality of the present Office Action be removed and that the Office clarify the rejection in the next official communication.

Claim 5 is amended herewith to likewise recite the absence of a membrane-permeabilizing reagent. Applicant respectfully submits that this amendment overcomes, for reasons already of record, the rejection of claim 5 as well as claims 8, 22-26 and 32, which depend, directly or indirectly, therefrom. Reconsideration and withdrawal of the rejection of claims 5, 8, 22-26, and 32 under 35 U.S.C. §102(b) as being anticipated by Low et al. (WO 90/12096), is accordingly requested.

The Office has also maintained the rejection of claims 1-8, 22-26, 29, and 32-35 as being clearly anticipated by Dargis et al. (Antimicrobial Agents and Chemotherapy, 38(5):973-980, 1994). This rejection is respectfully traversed.

Claims 1, 3 and 5, from which claims 6-8, 22-26, 29 and 32-35 depend, directly or indirectly, have been amended to recite that the biotinylated compound is delivered into the cytosol of the cell. Claims 2 and 4 have been canceled, insofar as the features of claim 2 and 4 have been incorporated into claims 1 and 3, respectively.

The Office suggests that because the biotinylated compounds taught in Dargis et al. cross the outer membrane, they must inherently get into the cytosol. Applicant respectfully disagrees, and sets forth below convincing evidence to the contrary.

To begin with, to get into the cytosol of a gram-negative bacterium, a compound must pass through (a) the outer membrane (i.e., the cell wall), (b) the periplasmic space, and (c) the inner membrane (i.e., the inner membrane).

Dargis et al. teaches β-lactams that pass through the outer membrane (cell wall). However, these β-lactams bind to specific targets in the inner membrane and become lodged therein. There is no teaching that the β-lactams proceed into the cytosol; to the contrary, Dargis et al. teach that β-lactams remain bound to membrane-associated binding proteins.

Specifically, Dargis et al. state that "β-lactam drugs must bind to specific targets *located in the cytoplasmic membrane* of bacteria to exert their inhibitory effects. These target proteins can be identified by their ability to *covalently bind* isotope-labeled penicillin and are termed penicillin-binding proteins (PBPs)" (Dargis et al., page 973, first col., emphasis added). These PBPs are "essential in the cross-linking of the bacterial cell wall" and "β-lactam antibiotics kill bacteria through inhibition of these . . . PBPs as substrate analogs of [a] component of peptidoglycan." (Dargis et al., page 973, first col., emphasis added). It is important to note that the PBP substrate (peptidoglycan) is located in the outer membrane.

The biotinylated reagent taught in Dargis et al. was able to label PBPs from isolated cytoplasmic membranes (Dargis et al., Fig. 3A, lane b, page 976), confirming that the target PBPs are present in the cytoplasmic membrane. Dargis et al. also showed that the biotinylated reagent labeled intact cells of *H. influenzae*, a gram-negative bacterium (Dargis et al., Fig. 3A, lane a, page 976). Binding was covalent (Dargis et al., page 975, second col.); β-lactam antibiotics interact covalently with PBPs at the active-site serine residue" (Dargis et al., page 978, second col.).

In summary, Dargis et al. teach that penicillin binding proteins (PMPs) are present *in the cell membrane*, not in the cytosol. They teach that the enzymatic activity of these PMPs takes place across the periplasmic space, *in the cell wall (outer membrane)*, not in the cytosol. The biotinylated reagent taught in Dargis et al., which inhibits this activity, mimics a peptidoglycan component of the outer membrane and *covalent binds* PMPs present in the inner membrane. Applicants respectfully submit that all relevant evidence in Dargis et al. points to a biotinylated reagent that covalently binds to a membrane-associate target *without* passing through the cell membrane. Dargis neither teaches nor suggests that the biotinylated β-lactams pass *through* the cell membrane and into the cytosol of the cell.

Moreover, in order to maintain a rejection under 35 U.S.C. §102(b) based on inherency, the Examiner must show that the inherent characteristic (in this case, passage of the biotinylated

β-lactam into the cytosol) *necessarily* flows from the cited art. Application of the principle of inherency is set forth out in MPEP 2112 (IV):

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is *necessarily* present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. *Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.*' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (emphasis added).

and further:

> "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)

The fact that "Dargis et al. did not study the amount [of biotinylated compound] in the cytosol" (Office Action mailed March 18, 2009, at page 3) provides no information or evidence as to whether there was, in fact, an amount of biotinylated compound in the cytosol to study. Applicants respectfully submit that the Examiner has not provided the necessary basis in fact to conclude that the biotinylated compounds were *necessarily* present in the cytosol of the cell.

Claims 1-8, 22-26, 29, and 32-35, as amended, recite that the biotinylated compound is delivered or taken *into the cytosol* of the cell. The presence of a biotinylated compound in the cytosol of a cell is not inherent in the teachings of Dargis et al. Accordingly, for at least these reasons, reconsideration and withdrawal of the rejection of claims 1-8, 22-26, 29, and 32-35 as

being anticipated by Dargis et al. is respectfully requested.

Rejection under 35 U.S.C. §103(a)

The Office has maintained the rejection of claims 1, 2, 5, 8, 21-26, 29, and 32-35 under 35 U.S.C. §103(a) as being unpatentable over Low et al. (WO 90/12096). The Office also maintained the rejection of claims 27 and 28 as being unpatentable over Low et al., as applied to claims 1-8, 21-26, 29, and 32-35, and further in view of Kim (U.S. Patent 6,322,788). These rejections are respectfully traversed.

Claims 1 and 5, as noted above in connection with the rejection under 35 U.S.C. §102(b), have been amended to recite the absence of a membrane-permeabilizing reagent. An analogous amendment was previously found by the Office to be persuasive for claims 3, 4, 6 and 7. For reasons of record, Applicant submits that claims 1 and 5, as amended, as well as claims 2, 5, 8, 21-26, 29 and 32-35 dependent therefrom, are nonobvious in view of Low et al. Reconsideration and withdrawal of the rejection of claims 1, 2, 5, 8, 21-26, 29, and 32-35 under 35 U.S.C. §103(a) as being unpatentable over Low et al. is respectfully requested.

Claims 27 and 28 depend, directly or indirectly, from claims 1, 3 and/or 5. Claims 1, 3 and 5 have been amended to recite the absence of a membrane-permeabilizing agent. For at least the reasons described above in connection with the rejections under 35 U.S.C. §102(b) and 35 U.S.C. §103(a), Applicant respectfully submits that the amended claims are not obvious over Low et al., and further in view of Kim (U.S. Patent 6,322,788). Reconsideration and withdrawal of the rejection of claims 27 and 28 as being unpatentable over Low et al., as applied to claims 1-8, 21-26, 29, and 32-35, and further in view of Kim (U.S. Patent 6,322,788) is respectfully requested.

Summary

It is respectfully submitted that pending claims 1, 3, 5, 7, 8, 21-29 and 32-35 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives at the telephone number listed below if it is believed that prosecution of this application may be in any way assisted or expedited thereby.

Respectfully submitted
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CERTIFICATE UNDER 37 CFR §1.8:
The undersigned hereby certifies that this Transmittal Cover Sheet and the paper(s), as described hereinabove, are being transmitted via the U.S. Patent and Trademark Office electronic filing system in accordance with 37 CFR §1.6(a)(4) to the Patent and Trademark Office addressed to **Mail Stop AF**, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 18th day of May, 2009.

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